UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,993	12/13/2001	Michael V. Wiles	R-948	4978

7590 12/05/2003

DELTAGEN, INC.
740 Bay Road
Redwood City, CA 94063

EXAMINER	
WILSON, MICHAEL C	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,993	WILES ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communicati n app ars on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-4,9,11-13,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8,10 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6-10-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II, claims 5-8, 10 and 14-18 is acknowledged.

Claims 1-4, 9, 11-13, 19 and 20 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claim Objections

Claim 10 is objected to because it is dependent upon claim 1 which is not under consideration.

Specification

The specification is objected to because the first line of the specification should state the application claims priority to US Provisional Application No: 60/256,195, filed 12-13-00.

The application numbers throughout the specification will require updating as necessary.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 5-8, 10 and 14-18 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility.

Claims 8 and 14-18 are directed toward a transgenic animal having a disruption of an alpha-endosulfine gene. The specification teaches making alpha-endosulfine -/- mice (pg 54). The specification suggests using the mice as a model of disease, specifically as a model for infertility, glucose metabolism, diabetes, behavioral, neurological, neuropsychological, psychotic phenotypes (pg 20-22; pg 22, lines 9-21). However, the specification does not disclose that infertility, glucose disorders, diabetes, behavioral, neurological, neuropsychological or psychotic disease found in humans is linked to a disruption in alpha-endosulfine. Glucagon deficient mice were subjected to the glucose tolerance test (GTT), insulin suppression test (IST) and glucose-stimulated insulin secretion test (GSIST) (pg 55-56; see especially pg 55, line 11); the mice claimed were not tested. Therefore, Example 4 (first occurrence; 2nd is on pg 57) does not relate to the claimed invention. Alpha-endosulfine -/- mice were also found to have less body weight than normal when fed a high fat diet (pg 57). The specification does not provide any use for such a mouse or how such a mouse correlates to any disease. The mice spent less time in the open field in the "open field" test (pg 57-58). The specification does not provide a use for such a mouse, that such results correlate to hyperactivity, or that a disruption in alpha-endosulfine is found in hyperactive humans. None of the phenotypes found by the tests correlate to a useful phenotype because the phenotypes described are not specific to a disease and are not linked to a disruption in

an alpha-endosulfine gene in humans. The results of the tests are also not statistically significant because the number of mice tested is not disclosed. The mice claimed cannot be used to determine compounds that modulate alpha-endosulfine expression (e.g. claim 11, not under consideration) because alpha-endosulfine is not expressed in the mice. Using the mice to determining whether a particular phenotype is ameliorated is not a specific or substantial utility because the specification does not link the phenotype to any specific disease or to a disease caused by a disruption in humans. The specification does not identify any compounds that ameliorate any condition using the mice. Thus, the specification does not provide a specific or substantial use for a mouse as claimed, specifically having a decreased body weight, "improved" glucose tolerance, blood glucose sensitivity to exogenous insulin, impaired glucose secretion while on a high fat diet or hyperactivity.

Claim 10 is included because it is directed toward making the mouse, which lacks utility for reasons above. Claims 5-7 and 9 are directed toward cells having a disruption of an alpha-endosulfine gene or a cell derived from the transgenic animal, and are included because the cells lack a specific and substantial utility for the reasons above and because the specification does not teach how to use the cells other than when they are part of a mouse that is a model of disease.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

> terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-8, 10 and 14-18 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use mice having abnormal pain threshold.

The specification does not teach how to make animals or cells having a disruption in an alpha-endosulfine gene other than mice. Specifically, claims 6 and 7 encompass mice and rat cells. "Murine" encompasses mice and rats (http://www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=murine). The only means of making a cell with a disruption in an alpha-endosulfine gene taught in the specification is by using mouse embryonic stem cell technology. The state of the art at the time of filing was such that embryonic stem (ES) cell technology had only been successful in mice. Wagner (May 1995, Clin. and Experimental Hypertension, Vol. 17, pages 593-605) and Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) taught germline transmission of ES cells has not been demonstrated in species other than mice and the growth of ES cells from species other than mice is unreliable. Wall (1996, Theriogenology, Vol. 45, pg 57-68) taught transgene expression and the physiological result of such expression in livestock was not always accurately predicted in transgenic mice (page 62, line 7). Since the time of filing, Zan (Nature Biotech, 2003, Vol. 21, pg 645-651) taught making knockout rats using mutagenized male rats, which was not taught in the specification

and considered essential to making knockout rats. The specification fails to provide sufficient guidance to make transgenics other than mice by teaching obtaining ES cells in species other than mice. The specification does not teach the nucleic acid sequence of an alpha-endosulfine gene in non-mice, non-human species or correlate the alpha-endosulfine gene in mice to the alpha-endosulfine gene in other species. The specification does not teach how to make knockout animals other than mice or correlate making knockout mice to other species. Therefore, the specification does not provide adequate guidance for one of skill in the art to make a transgenic, non-human animal or cells having a disruption in an alpha-endosulfine gene in any species other than mice.

The specification does not provide adequate correlation between the phenotype obtained in mice to the phenotype obtained in other species. The state of the art at the time of filing was that the phenotype of transgenic mice does not predict the phenotype in non-mice species. Models of human diseases have relied on transgenic rats when the development of transgenic mice having the desired phenotype was not feasible. Mullins (1990, Nature, Vol. 344, pg 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse Ren-2 renin transgene. Hammer (1990, Cell, Vol. 63, pg 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human b_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989, EMBO, Vol. 8, pg 4065-4072; Taurog, 1988, J. Immunol., Vol. 141, pg 4020-4023) expressing the same transgenes that successfully

caused the desired symptoms in transgenic rats. Therefore, the specification does not enable making transgenic having the disclosed phenotypes in species other than mice.

In addition, claims 14-18 do not provide a nexus between the disruption in alpha-endosulfine and the phenotypes claimed. The claims do not recite the disruption of alpha-endosulfine causes the phenotype claimed. The specification does not teach disrupting the alpha-endosulfine gene in mice already lacking production of alpha-endosulfine or in mice already having the phenotypes recited in claims 14-18. Given the art of transgenics at the time of filing taken with the guidance provided in the specification, the claim should reflect the fact that the phenotypes recited in claims 14-18 are a result of alpha-endosulfine disruption. Otherwise, it would require one of skill undue experimentation to make the mouse as broadly claimed.

The specification does not enable making or using a transgenic with a wild-type phenotype as encompassed by claim 8. The transgenic of claim 8 does not recite any phenotype and may, therefore, have any phenotype including wild-type phenotype. The specification does not provide any use for a transgenic having a disruption in an alpha-endosulfine gene that has a wild-type phenotype. The only disclosed phenotype for the transgenic claimed is one that correlates to a disruption in an alpha-endosulfine gene. Therefore, the claims should recite a non-wild-type phenotype that correlates to a disruption in an alpha-endosulfine gene.

Claim 10 is directed toward a method of making a transgenic mouse having a disruption in alpha-endosulfine using a mouse ES cell having a disruption in an endogenous alpha-endosulfine gene, introducing the cell into a mouse blastocyst,

implanting the blastocyst into a pseudopregnant mouse which gives birth to chimeric mice, and breeding the chimeric mouse to produce the transgenic mouse. The claim does not require using mouse cells or an embryonic stem cell, which are considered essential to the invention. A mouse ES cell is the only type of cell taught in the specification that can be introduced into a blastocyst and result in a chimeric mouse as claimed. The claim does not require the mouse have a non-wild type phenotype, which is required for reasons cited above. Given the unpredictability in the art taken with the guidance provided in the specification, the cell in a) should be a mouse ES cell, the blastocyst in b) should be a mouse blastocyst, and the transgenic mouse produced should have a genome comprising a homozygous disruption in an alpha-endosulfine gene, wherein said disruption causes a disclosed phenotype.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-8, 10 and 14-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of what applicants consider "alpha-endosulfine" genes cannot be determined. The specification defines the term as any gene of SEQ ID NO:1 or having homology to SEQ ID NO:1 (pg 9, lines 1-4). However, not all genes sharing homology with SEQ ID NO:1 are GPRC5-like genes. For exampleARPP-19 shares

homology with SEQ ID NO:1, but is not an alpha-endosulfine gene (Heron, 1998, PNAS, Vol. 95, pg 8387-8391; pg 8387, col. 2, lines 8-11).

Claims 14-18 are indefinite because they do not clearly set forth that the disruption in alpha-endosulfine causes the phenotype.

Claims 15-18 are indefinite because they require improved glucose tolerance, sensitivity to insulin, impaired glucose secretion or hyperactivity, which are all relative conditions, but do not the require comparison to another type of mouse. The metes and bounds of mice encompassed by the claims cannot be determined because it is unclear to what the mice claimed are being compared.

The metes and bounds of what applicants consider improved glucose tolerance cannot be determined (claim 15). The phrase "glucose tolerance" is not defined in the specification and does not have an art recognized definition. Therefore, it cannot be determined how glucose tolerance is improved.

The metes and bounds of what applicants consider "glucose sensitivity to... ...insulin" cannot be determined (claim 16). The phrase is not defined in the specification and does not have an art recognized definition. The metes and bounds of what applicants consider "glucose sensitivity" cannot be determined.

The metes and bounds of what applicants consider "impaired glucose sensitivity" cannot be determined (claim 17). The phrase is not defined in the specification and does not have an art recognized definition. The metes and bounds of what applicants consider "impaired glucose sensitivity" cannot be determined.

The metes and bounds of what applicants consider "hyperactivity" cannot be determined (claim 16). The phrase is not defined in the specification and does not have an art recognized definition. The metes and bounds of what applicants consider "hyperactive" cannot be determined. How active is hyperactive?

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (Scientific American, 1994, Vol. 270, pg 34-41) in view of Versolvy-Vergine, Diabetologia, 1996, Vol. 39, pg 135-141).

Capecchi taught making a mouse having a disruption in a gene. Capecchi did not teach disrupting the alpha-endosulfine gene.

However, Versolvy-Vergine taught the nucleic acid sequence of the mouse alpha-endosulfine gene.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic mouse having a disruption in a gene as taught by Capecchi wherein the gene was alpha-endosulfine as taught by Versolvy-Vergine. One of ordinary skill in the art at the time the invention was made would have

been motivated to disrupt the alpha-endosulfine gene instead of the gene disrupted by Capecchi to determine the function of alpha-endosulfine *in vivo*.

Thus, Applicants' claimed invention, as a whole is prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

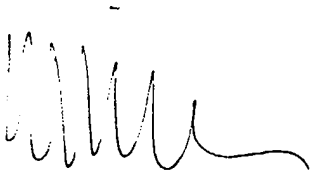
Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER